ABSTRACTS

On the Nature of the Mitsuda and the Kveim Reaction, **R. Kooij** and **T. Gerritsen,** Dermatologica, Basle, **116**, No. 1, 1958, pp. 1–27.

After a review of the work of previous authors on the lepromin and Kveim reactions, the authors recall that they themselves obtain positive lepromin reactions with normal tissue particles (Int. J. of Leprosy, **24,** 1956, p. 171), and after concentration and centrifugalization of the normal tissue preparations the strength and specificity of the reaction had decreased. This suggested to them the hypothesis that in the Mitsuda reaction the presence of particles and the size of them might be the important factor, and the Mitsuda is in effect a foreign body reaction or isomorphic phenomenon. *In their first experiment* they tested a suspension of particles from normal liver, prepared by the Dharmendra method, against lepromin from lepromatous ear lobes and lepromin from lepromatous liver and spleen, on 10 tuberculoid patients. The preparation from normal liver gave positive results in tuberculoid leprosy, and negative in lepromatous leprosy, and the reactions were similar to those from the lepromins. *In the second experiment* they tested various preparations of normal liver for activity. That obtained by the Mitsuda-Wade method was nearly inactive, but when it was concentrated 12 times the reactivity almost doubled. A Dharmendra preparation from normal liver, 25 times concentrated, resulted in even stronger Mitsuda reactions, and the strongest were obtained with a Dharmendra preparation 100 times concentrated. With the concentrated preparations the lepromatous form of leprosy showed negative results. *In the third experiment* they compared the activity of the 100 times concentrated Dharmendra preparation from normal liver with that of lepromin made by the Mitsuda-Wade method from lepromatous ear lobes, and of another similar lepromin made from lepromatous liver. They found that the preparation derived from normal liver behaved very like the others, though somewhat weaker, but it could be used as a standard preparation. *In their fourth experiment* they studied the importance of the particulate state of the preparation, using bacterial filtrates (Seitz) of (*a*) the Dharmendra preparation from lepromatous earlobes; (*b*) the 25 times concentrated Dharmendra preparation from normal liver; (*c*) a crude preparation from lepromatous liver, obtained by the Mitsuda-Wade method. The results of the average readings showed that the particulate nature is essential for the Mitsuda reaction. *In their fifth experiment* they tested several Kveim antigens on both tuberculoid and lepromatous patients, comparing them with Mitsuda-Wade preparation from normal liver; the results were all very similar. All the Kveim preparations showed weak or negative reactions in lepromatous leprosy and positive results in tuberculoid. In the latter biopsies showed histologically a tuberculoid structure.

The authors conclude that the Kveim antigen does not contain a specific substance and the reaction produced is similar to that of a saline nature. Probably the Kveim reaction differs only quantitatively in healthy people, patients with sarcoidosis, tuberculoid leprosy, and perhaps some other diseases: it is an expression of a sarcoid mode of reaction in certain individuals, and the disease sarcoidosis is a syndrome which can be evoked by many agents. The Mitsuda reaction also seems a sarcoid (tuberculoid) form of foreign body reaction, or an isomorphic phenomenon. It seems to be a general tissue response to foreign bodies, such as leprosy bacilli, normal tissue particles, etc. The tuberculoid or sarcoid mode of reaction may be a general predisposition on the part of certain individuals, and infants and growing children develop it as part of a normal maturation cycle. The absence of the Mitsuda reaction in the lepromatous type may be due to a fault in the reticulo-endothelial system. More study of the Mitsuda reaction and the causes of its absence in the lepromatous may lead us to a better understanding of the pathogenesis of leprosy.

Effect of BGC Vaccination, Lepromin Testing, and Natural Causes in Inducing Reactivity to Lepromin and to Tuberculin. **J. A. Doull, R. S. Guinto, and M. C. Mabalay.** Int. J. of Leprosy, **25,** No. 1, Jan.–Mar. 1957, pp. 13–37.

The authors carried out field work of 7 months in the island of Mactan, Philippines, on a selection of healthy children; there were 550 between the ages of 6 and 35 months. As a control group, an artificial arrangement of 110 sets of 5 children was set up. The inoculations of PPD-S, BCG, lyophilized BCG, diphtheria toxoid, saline, and lepromin were carefully grouped and planned to determine the relative importance of natural causes, initial lepromin testing, and BCG vaccination in producing reactivity to lepromin and to tuberculin. The results tended to show that increase in frequency of reactivity to lepromin in subjects vaccinated with BCG cannot be attributed to the vaccination with BCG alone. Natural causes contribute, and this natural reactivity to lepromin is not necessarily due to infection with *M. leprae.* Infection with *M. tuberculosis* is also an inadequate explanation.

Significance of the Relationship Between the Lepromin and Tuberculin Reactions in Leprosy Contacts. **N. Souza Campos, J. Rosemberg,** and **J. A. Aun.** Int. J. of Leprosy, **25,** No. 1, Jan.–Mar. 1957, pp. 38–48.

They studied children in preventoria and carried out tuberculin and lepromin tests on them. These children had been exposed to leprosy infection, for their parents were leprosy patients. The authors found evidence of the existence of a state of specific resistance or immunity due to the attack by leprosy infection, as well as a state of cross resistance due to tuberculous infection. They analyse the situa-

tion in contacts by distinguishing between those with a state of "leprosy infection" and a state of "leprosy disease." Some contacts are lepromin-positive and have either or both a specific resistance and cross resistance; they may appear to be free of morbidity or show tuberculoid lesions. Other contacts are lacking in resistance and are lepromin-negative; there may be no sign of morbidity or there may be indeterminate or lepromatous lesions. The authors also found that the incidence of leprosy among close contacts is much lighter than suggested by general epidemiological data. They think that priority in care and consideration should be given to lepromin-negative and tuberculin-positive children, and next to lepromin-negative and tuberculin-negative children. They noted a high frequency of positive lepromin reactions in subjects without apparent leprosy, and a high incidence of tuberculoid lesions among the close contacts with open forms of leprosy, and suggest the possibility of the existence of a lymphatic system infection in which clinical signs are absent, and the true onset of leprosy is shown by the visible or detectable clinical manifestations.

Is Erythema Nodosum Leprosum a Favourable Occurrence? **A. R. Davison and R. Kooij.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 91–98.

The authors incline to the view that e.n.l. is a form of panniculitis and confirm its great increase since sulphone therapy began to be used. They find it is not a reaction to one class of drugs, but is provoked by all drugs which are active against leprosy; yet it is not a reaction to the drug treatment alone, for it does not occur in non-lepromatous cases under any type of treatment. From their study of 200 patients with e.n.l. and 142 without it they derive strong evidence that it is not a favourable sign in the course of leprosy. In the e.n.l. cases the average period of treatment until arrest of the disease was significantly longer, and the bacteriological index much higher and took longer to reach negativity. A mild degree of e.n.l. retarded the arrest of the disease as much as did a severe degree. The incidence of e.n.l. increased with the duration of the disease. The cause of e.n.l. remains obscure: it resembles the Herxheimer reaction, although the attacks last longer and may recur for years. If it is a kind of panniculitis, it is not surprising to find it is an unfavourable reaction which should be controlled.

Chemotherapy of Murine Leprosy. **Y. T. Chang.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 130–145.

A total of some 25 chemical compounds related to INH have now been studied in tuberculosis by other workers. The most successful in mouse tuberculosis was Compound 337, which is isonicotinyl-hydrazone of 2-carboxymethoxybenzaldehyde, reported on by Siebenmann and Zubrys. A related compound, also with high activity and low toxicity, is Compound 373, which is isonicotinyl-

hydrazone of 2-carboxymethoxy-3-methoxybenzaldehyde. Chang now reports on studies of their effects in mouse leprosy, compared with INH. Compound 337 in continuous administration for 15 months suppressed the infection in the majority of the mice. This is the first drug to do so for so long. Compound 373 and INH were highly active for the 3 months trials, but rather less effective than Compound 377. For all three compounds the suppressive activity over 3 months was not permanent, for when the drug was stopped the disease showed itself again, and caused death.

Effect of X-Ray Irradiation on Excised Earlobe Specimens from Cases of Lepromatous Leprosy. **A. Mukherji.** Int. J. of Leprosy, **25,** No. 2, April–June 1957, pp. 147–149.

Previous work on the application of X-rays to destroy *M. leprae* used high doses for a short time and the result was neither a permanent cure nor any change in the bacteriological picture. Mukherji therefore has used prolonged irradiations in mild doses (63r to 84r over periods of 45 to 60 minutes for 3 to 4 successive days). Smears and histological preparations from pieces of excised lepromatous earlobes thus irradiated showed marked reduction in numbers and beading and disintegration of the leprosy bacilli, and no damage to tissue cells. This suggests practical value as a therapy of local or general lesions.

Patogenia de la Lepra Reacción Lepromatosa (*Pathogenesis of the Lepromatous Lepra Reaction*) **A. J. Melamed.** Leprología, Buenos Aires, **1,** No. 2, July–Dec. 1956, pp. 167–173.

The author's thinking centres round the concept of the lepromatous lepra reaction as a manifestation of sensitivity on the part of the lepromatous tissues which places it in the group of fixed vascular reactions, which also includes periarteritis nodosa. There is clinical and experimental evidence for this. When lepromatous tissue is conditioned or ready to react it is in a state of critical equilibrium with regard to the corticosteroids or conditions such as are brought about by them. Thus every stress factor, such as would increase the consumption of the corticosteroids in the body, would provoke or increase the lepra reaction. It follows that preventive treatment of lepra reaction is preferably directed to removing stress factors and to protecting lepromatous tissue by small continuous dosage of glucocorticoids and other medicaments of similar action.

Mecanismo de la Actividad Antileprotica de las Sulfonas (*Mechanism of the anti-leprosy action of the sulphones*). **M. Bergel,** Leprología, Buenos Aires, **1,** No. 2, 1956, pp. 156–166.

The author reviews the classification and pharmacology of the sulphones used against leprosy, and describes experiments which show the anti-oxidant action of DDS *in vitro* and *in vivo*. He interprets the anti-leprosy action of the sulphones as an anti-oxidant action conferred on them by their amines which stabilize the fats of

the body. In his experiments the addition of 2 in 1,000 of DDS to a diet low in Vitamin E content and containing 15% by weight of linseed oil prevented in rats the peroxidation and polymerization of the subcutaneous fat, as well as of the peri-renal and perigonadal, whereas it took place in the control animals and produced "yellow fat". DDS in the digestive tract averts the oxidation of the small amounts of Vitamin E used in the experimental diets and thus also averts the peroxidative process: also DDS is absorbed and deposited in the fatty tissues and acts as a biological anti-oxidant, replacing the biological activity of the tocopherols in their anti-oxidant capacity. DDS and related compounds (e.g. DDSO) owe their chemotherapeutic value against leprosy to the primary and direct action of their amines which confer this anti-oxidant action, which augments the stability of the lipids of the body. This makes them non-specific agents, for the action is not on the bacilli but on the tissues of the body. By contrast the sulphonamides have a direct antibacterial action on cocci.

Reaction States in Leprosy. **R. Chaussinand,** "Prophylaxie et Thérapeutique de la Lèpre", published by Bibliotheque de Thérapeutique Médicale, Paris, 1958. pp. 66–70.

The subject of reaction states is one of the sections of this booklet by Chaussinand. He thinks that reaction in leprosy probably is provoked by a sensitization of the body to disintegration products of the leprosy bacillus. Tuberculoid leprosy is allergic in nature, and here the sensitization seems to augment the natural resistance and to lead in the end to improvement in the skin lesions, though often enough to an increase in nerve damage. True reaction states do not occur in indeterminate leprosy, but in the anergic lepromatous type the reaction is the most violent, with fever, cachexia, arthalgia, neuritis, ocular lesions, and an increase in cutaneous and mucous lesions. It may even be fatal in the lepromatous if the reaction is long lasting or recurrent. Large doses of sulphones or a too rapid increase in dosage may unchain the reaction. There have been many treatments advised for the control of the condition but none is constantly effective. The author describes many of these and at the present time finds the most effective are *Hydrocortancyl* and *Anthiomaline*. The former is a synthetic steroid, delta-1-dihydrocortisone which has very strong anti-inflammatory and anti-allergic properties. He begins with an oral dose of 30 mgm. and keeps this up for a week or more at need. The sulphone therapy can also be kept going on a slightly less dose, and there should be a low salt diet. The treatment can be repeated in case of relapse. In those cases with repeated reactions one can lead off with Hydrocortancyl and follow with a series of Anthiomaline injections. Anthiomaline is given by intramuscular injections in increasing doses of 6 to 24 cg. per injection three times a week for 3 to 4 weeks.

Fator "N" de resistência à lepra relações com a reatividade lepromínica e tuberculínica: valor dudivoso do BCG na imunização anti-leprosa (*The "N" factor of resistance to leprosy and its relation to the reactivity to the lepromin and tuberculin tests: the doubtful value of BCG in immunization against leprosy*). **A. Rotberg.** Revista Brasil. de Leprol. **25**, 2, April–June 1957, pp. 85–106.

In 1937 the author first suggested the possible existence of a specific factor "N" which governs the resistance to leprosy, and in this paper he marshals the observations of other workers and his own, and the reasoning from them, which lead to a strengthening of the belief in the existence of this factor. He starts from the assumption that a positive lepromin test (LT) indicates a resistance to leprosy, and this is generally agreed. Most children are negative to the LT but later spontaneously become positive. There is no known factor behind this change in reactivity: the small fraction of adults who remain negative to the LT constitute an "anergic fringe" and cannot be distinguished from the positive majority except by the result of the LT itself. Child contacts may show differences in reactivity. It all points to the existence of a constitutional factor which governs essentially the individual capacity to react specifically to the leprosy bacillus. In epidemiology and prevention of leprosy the "anergic fringe" has great practical importance, for this group gives rise to the lepromatous cases. Under the impact of secondary factors, such as debilitating and other unknown conditions, the anergic leprosy-infected individual may change into an active case of lepromatous leprosy.

The author then reviews the immunological relationship between leprosy and tuberculosis. (1) He thinks that tuberculous infection or disease alone will not produce a positive LT without the influence of "Factor N". This is the real reason why lepromatous cases, all practically negative to LT, are yet 50 to 80% positive to tuberculin. There are always some individuals who remain lepromin-negative despite active tuberculosis or tuberculin sensitivity, and they form a narrow fringe of much the same size as the "anergic fringe" referred to above. Therefore the author disagrees with the idea that tuberculosis contributes to the limitation of the endemic of leprosy. On the contrary he thinks it may become one of the secondary factors capable of aggravating an existing leprosy or setting off a latent one. (2) Neither can BCG interfere with the "anergic fringe". In some healthy subjects or active or involuted lepromatous cases lacking "Factor N" it does not produce positivity of the LT. (3) But when the specific "Factor N" is present, leprosy, tuberculosis, BCG, and some other possible factors often produce lepromin-positivity. This would explain the positive LT in non-leprosy areas, and the conversion in children of a percentage of negative LT to positive by BCG.

In this case the BCG artificially and precociously converts the lepromin status of individuals who possess the "Factor N" and who would become lepromin-positive spontaneously in the natural course of events. This anticipation of reactivity might have a clinical value in later leprosy but in prevention and control of the disease BCG is of importance only if it really reduces "anergic fringe", as shown by producing 2 and 3 plus LT in a significantly higher percentage of individuals as compared with the spontaneous lepromin conversion.

Lepromin-reaçao em Holandeses radicados ha 2–3 anos no Brasil e sem contacto conhecido com doentes de lepra (*The Lepromin Reaction in Dutch people settled for* 2–3 *years in Brazil and without known contact with leprosy patients*). **L. M. Bechelli, R. Quagliato,** and **S. J. Nassif.** Revista Brasil. de Leprol. **25,** 2, April–June 1957, pp. 107–125.

A group of immigrant Dutch families, mostly farm-workers, gave an opportunity for study of the lepromin reaction in individuals originating in a part of Europe where leprosy is practically extinct. Mantoux and lepromin tests were made in 240 Dutch people and 89 indigenous schoolchildren who were living in the same environment (which are free of known foci of leprosy). In the Dutch the age groups 0 to 9 years had 80% negative to the LT, and age groups 10 to 19 years had 50 to 60% negative. The higher positives of 2 plus and 3 plus were not found between 0 and 9 years, but from 10 to 19 years such were found in 15 to 20%, and up to 40% in the later ages. The Brazilian children had smaller percentages of negative LT, namely 53% for 5 to 9 years and 30% for 10 to 14. When correlating with the tuberculin test it was noted that 70 to 80% lepromin positivity may go along with Mantoux negativity, and the positivity of the Mantoux does not seem to influence the lepromin positivity. The authors think that the positivity of the LT in these Dutch immigrants may be explained by their possession of Rotberg's "N Factor", though in some cases there may be a cross sensitization to the bacillus of tuberculosis.

The Classification of Leprosy in Japan as described by the Council for Leprosy Research, June 18th, 1956, appears in La Lepro, **25,** Oct. 1956 (Selected Articles) pp. 91–96.

Japanese leprologists conferred on the question of standardization of classification and agreed on the following:—

The types of leprosy are two only, Lepromatous (L) and Tuberculoid (T), but the latter has two subtypes, tuberculoid macular (TM) and Tuberculoid neural (TN). Cases which are indeterminate as L or T are classified tentatively as Group A (atypical) and at subsequent repeated examinations efforts are made to take them out of the atypical group and assign them to L or T. The L type is marked by the following features; smears contain many leprosy bacilli and often globi; the skin has a typical thickening and shade

of colour, and eyebrows depilate; the lepromin test is usually negative; lepra cells occur in tissue sections. The L type is stable and does not change to others. Of the T type, the TM subtype has usually negative smears for bacilli, the skin lesions are hyperaemic and elevated (occasionally not elevated), the lepromin test is usually positive, and histologically the lesion shows a lymphocytic and epithelioid cell infiltration and often giant cells, but no lepra cells; the colour of the lesions is often helpful in differentiating from the L type. (There is no mention of the useful clinical indicator provided by symmetry or asymmetry of the localization of the lesions on the body: the former suggests lepromatous). In the TN subtype, sensory or motor nerve disturbances are prominent, and the only skin lesion which is allowed in this subtype is the hypopigmented macule.

Progressive and retrogressive stages (p and r) are recognized for all, and various clinical and laboratory evidence is sought for them; likewise there is a quiescent stage (q). There is a notation devised for extent of lesions, nerve damage, and mutilations.

Infectivity of Non-lepromatous leprosy. **T. N. N. Bhatta Thiripad,** Leprosy in India, **29,** 2, April 1957, pp. 39–43.

The author discusses the question of the possibility of the infectivity of the supposed closed case, and adopts a cautious attitude, pointing out the difficulty of being sure of the non-infectivity of such cases and on the other hand how often the only possible infecting agent seems to be a closed case. He describes two illustrative cases which seemed to derive their infection from a closed case. He thinks that from the point of view of public health and control of leprosy it is safer to consider all cases of leprosy which are active to be possible infecting agents, especially in these days when we possess an effective remedy and can arrest all types.

Treatment of Dermatitis Herpetiformis with DDS, **N. S. Smelov** and **V. A. Laptev,** Vestnik Dermatologii i Venerologii, Moscow, 1958 No. 2, pp. 7 to 11.

The authors treated 13 patients suffering from dermatitis herpetiformis with daily doses of 100–200 mgm. of DDS, in three to four courses of 6 days. They noted that the treatment was effective in controlling the skin lesions and was particularly good in soothing itch, which is so prominent in this disease.